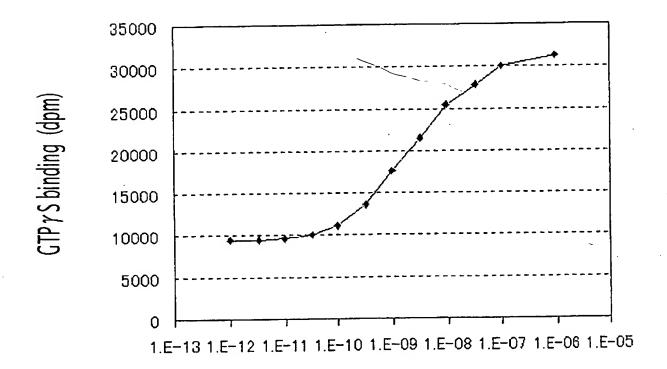


Fig. 2



GPR 8 ligand [M]

Fig. 3

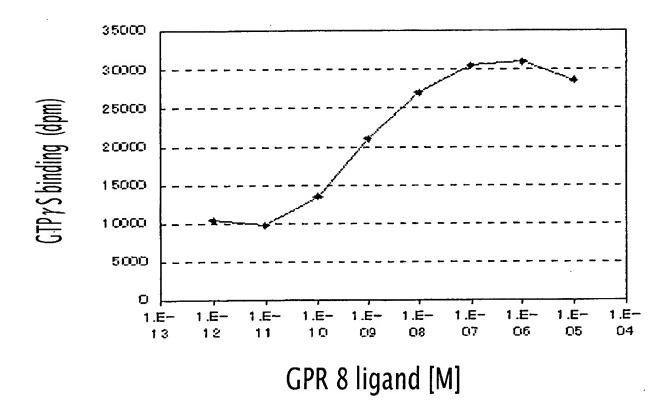
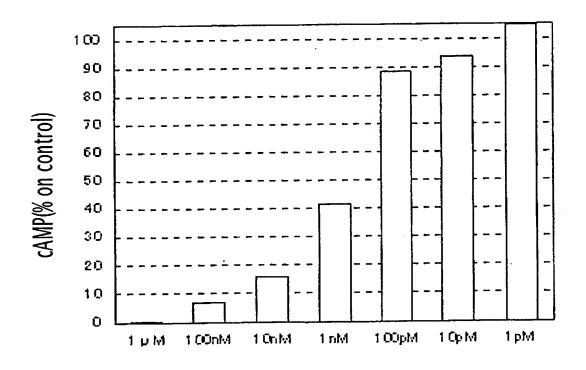


Fig. 4



GPR 8 ligand

Fig. 5

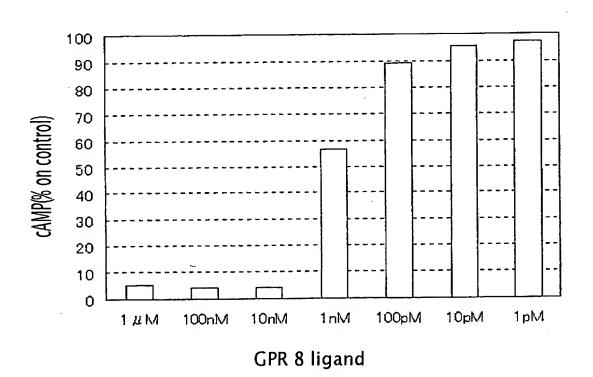


Fig. 6

						GGC	GGG	GCC	VCC	GAG	CGG	ATT	TAG	CTG	GGC	CTG	CAG	GGG	ACC	42
240	ccc	ፐርር	ССТ	CCA		TCC														102
CAL		100	ccc	CAG	cce	GTT	CGT	GGC	CCG	CCC	CGC	CGG	GCG	GCC	GTC	GAC	GCG	AGC	GCC	162
LLA	AAC	CUA	GCC	Ono	CCU	GII	001	000												
050	000	TCC	cc.c	CCA	ccc	GAG	CGG	GGG	GCT	CCC	GCG	AGC	CGG	CCG	CGG	CTG	GCA	CTG	CTG	222
	43.5	T	LGC	Dea	GOO.	Glu	Aro	Glv	Ala	Pro	Ala	Ser	Arg	Pro	Arg	Leu	Ala	Leu	Leu	20
Leu	МIЯ	11.b	Arg	110	Oly	010	711 B	01,												
- TrΩ	CTT	ርተር	CTC	CTG	стс	CCG	CTG	CCC	TCC	GGC	GCG	TGG	TAC	AAG	CAC	GTG	GCG	AGT	CCC	282
CIG	Lau	Lau	Len	len	Len	Pro	Leu	Pro	Ser	Gly	Ala	Trp	Tyr	Lys	His	Val	Ala	Ser	Pro	40
Leu	Leu	Leu	Leu	DCD	202			•		•										
CGC	TAC	CAC	ACG	GTG	GGC	CGC	GCC	GCT	GGC	CTG	CTC	ATG	GGG	СТС	CGT	CGC	TCA	CCC	TAT	342
Arp	Tvr	His	Thr	Val	Gly	Arg	Ala	Ala	Gly	Leu	Leu	Met	Gly	Leu	Arg	Arg	Ser	Pro	Tyr	60
	-,-																			
CTG	TGG	CGC	CGC	GCG	CTG	CGC	GCG	GCC	GCC	GGG	CCC	CTG	GCC	AGG	GAC	ACC	CTC	TCC	CCC	402
Leu	Trp	Arg	Arg	Ala	Leu	Arg	Ala	Ala	Ala	Gly	Pro	Leu	Ala	Arg	Asp	Thr	Lev	Ser	Pro	80
GAA	CCC	GCA	GCC	CGC	GAG	GCT	CCT	CTC	CTG	CTG	CCC	TCG	TGG	GTT	CAG	GAG	CTG	TGG	GAG	462
Glu	Pro	Ala	Ala	Arg	Glu	Ala	Prp	Leu	Leu	Leu	Pro	Ser	Trp	Val	Gln	Glu	Leu	Trp	Gl v	100
ACG	CGA	CGC	AGG	. AGC	TCC	CAG	GCA	GGG	ATC	ccc	GTC	CG7	GCG	CCC	CGG	AGC	CCG	CGC	GCC	522
Thr	Arg	Are	Are	g Ser	Ser	Glr	Ala	Gly	Ile	Pro	Va]	Arg	Ala	Pro	Arg	Ser	Pro	Arg	Ala	120
CCA	GAG	CCT	CCC	CTC	GAA	CCC	GAC	TCC	CTO	GAC	TT(AGG	G GG#	GC1	r GG(CAC	G AGA	CTI	CGG	582
Pro	Glu	Pro	Ala	a Lei	1 Glu	ı Pro	Gli	Sea	Lei	ı Ası	Phe	e Set	r Gly	, Al:	a Gl	, Gli	n Arg	g Let	Arg	140
AGA	GAC	GTO	C TC	C CGG	CCA	A GC	GTO	G GAC	CCC	GC	A GC	A AA	C CGG	C CT	T GG	C CT	G CC	C TGC	CTG	642
Arg	, Ası	Va.	l Se	r Ar	g Pro	o Ala	a Val	l Asj	o Pro	Al:	a Ala	a Asi	n Arı	g Le	ن G1	y Le	u Pro	Cy:	s Leu	160
GC	CCC	C GG.	A CC	G TT	C TG	A CA	G CG	L CC	c cc	G CC	C GC	C CG	T GG	C GC	c tc	C GC	G CC	T GAG	C CCA	702
	a Pro																			165

GGA GGA GTG GCC GCG CG

719

Fig. 7

					CC	TCC	GGA	GCC	AGT	TCC	TGG	TCC	GCC	CCG	CCG	GGA	GCC	GTC	AGC	44
ATG Met	AAC Asn	CCC Pro	CGG Arg	GCA Ala	CGC Arg	GGC Gly	ATG Met	GGA Gly	GCG Ala	CGG Arg	GGC Gly	CCG Pro	GGA Gly	CCG Pro	GGG Gly	GCC Ala	ACT Thr	GCG Ala	AGG Arg	104 20
CGC	CGG	CTG	CTG	GCA	TTG	CTG	ATT	CTG Leu	CTG	CTG	CTG	CTG	CCG	CTG	CCC	GCC	CGT	ecc	TGG	164 40
TAC Tyr	AAG Lys	CAC His	ACG Thr	GCG Ala	AGT Ser	CCC Pro	CGC	TAC Tyr	CAC His	ACG Thr	GTG Val	GGC Gly	CGC Arg	GCC Ala	GCG Ala	GGC Gly	CTG Leu	CTC Leu	ATG Met	224 60
								TGG Trp												284 80
GCC Ala	TGG Trp	GAC Asp	ACT Thr	TTC Phe	GGC Gly	CAG Gln	GAC Asp	GTG Val	CCC Pro	CCT Pro	CGG Arg	GGA Gly	CCC Pro	TCC Ser	GCC	AGG Arg	AAC Asn	GCC	CTC Leu	344 100
								GCT Ala												404 120
CAG Gln	GTG Val	CGA Arg	CGC	GGA	AGC Sei	TTC	CGC	TCC Ser	GGG Gly	ATC	CCG	GTC Val	AGT Ser	SOS '	CCC Pro	CGC Arg	AGC Ser	CCG Pro	CGC Arg	464 140
GCC	CGG	660 613	TCC	GAC	CCC	G CAA	CCC	G GAA	TTC	G GGC	GCC Ala	TCI Sei	TCC Ser	TGC	G ACC	TCC Sei	GCC Ala	GAG	7AG 1 ***	524 159
ACC	C AGA	GC(C TTO	C GG/	A GA(TC1	r TC	A GCI	CAC	G CGC	TG0	TC	r GC							565

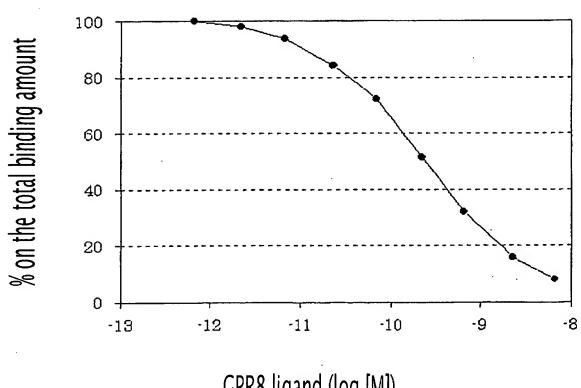
Fig. 8

								TGT	AGT	CGC	ACC	AAC	TGA	CTA	GTC	TCT	TCC	ATC	CTC	36
CGG	AGC	TCC	GAC	GTT	CTC	GGG	GAC	ATA	AAC	CCT	GTT	CTT	GTC	CTA	ACC	CGC	CAA	GGG	GCC	96
ΛTG	GAC	TTG	AGC	GCG	CTG	GCG	TCG	ΛGC	AGA	GAA	GTA	CGG	GGC	ССТ	GGG	ссс	GGG	GCT	CCG	156
Met	Asp	Leu	Ser	Ala	Leu	Ala	Ser	Ser	Arg	Glu	Val	Arg	Gly	Pro	Gly	Pro	Gly	Ala	Pro	20
GTG	AAC	CGG	CCC	CTG	СТА	CCG	CTA	CTG	CTG	CTT	СТG	СТС	TTG	CTA	ССТ	CTG	ccc	GCC	AGC	216
Val	Asn	Arg	Pro	Leu	Leu	Pro	Leu	Lev	Pro	Lev	Pro	Ala	Ser	· 40						
						GCG														276
Ala	Trp	Tyr	Lys	His	Val	Ala	Ser	Pro	Arg	Tyr	His	Thr	Val	Gly	Arg	Ala	Ser	Gly	Leu	60
стс	ATG	GGG	CTG	ccc	CGC	TCG	ccc	TAC	CTG	TGG	CGC	CGT	GCC	TTG	GGT	GGG	GCC	GCT	GGA	336
Leu	Met	Gly	Leu	Arg	Arg	Ser	Pro	Tyr	Leu	Trp	Arg	Arg	Ala	Leu	Gly	Gly	Ala	Ala	Gly	80
CCG	стс	GTG	GGG	СТС	CCG	GGA	CAG	ATG	GCC	CGC	AGC	GCT	СТС	CTG	CT T	ССТ	TCC	CCC	GGG	396
Pro	Leu	Val	Gly	Leu	Pro	Gly	Gln	Met	Ala	Arg	Ser	Ala	Leu	Leu	Leu	Pro	Ser	Pro	Gly	100
CAG	GAG	CTG	TGG	GAG	GTA	CGA	AGC	AGG	AGT	TCA	CCG	GCA	GGA	CTT	ССС	GTG	CAT	GCA	ACC	456
Gln	Glu	Leu	Trp	Glu	Val	Arg	Ser	Arg	Ser	Ser	Pro	Ala	Gly	Leu	Pro	Val	His	Ala	Thr	120
CGG	AGT	CTG	CGG	GAC	CTG	GAG	GGA	GCC	GGC	CAA	ССТ	GAG	CAG	TCG	CTA	AGC	TTT	CAG	TCC	516
Arg	Ser	Lev	Arg	Asp	Leu	Glυ	Gly	Ala	Gle	Gln	Pro	Glu	Gln	Ser	Leu	Ser	Phe	Gln	Ser	140
TGG	ACT	TCA	GCA	GAG	CCC	GCT	GCT	AGA	GCC	TTC	GGT	GAG	ACG	CTT	CGT	GCC	CAG	CCA	TGG	576
Trp	Thr	Ser	Ala	Glu	Pro	Ala	Ala	Arg	Ala	Phe	Gly	Glu	Thr	Leu	Arg	Ala	Gln	Pro	Trp	160
TTC	CTG	CAG	CAA	ATC	АТС	TTT	GCC	GAT	CCT	GTC	AGG	CTC	GAC	GAC	CGT	СТС	AAG	AAC	CGA	636
Phe	Leu	Gln	Gln	Ile	Ile	Phe	Ala	Asp	Pro	Val	Arg	Leu	Asp	Asp	Arg	Leu	Lys	Asn	Arg	180
TGG	CGC	CCC	CGT	GCŤ	TGA	CCT	AAG	CAG	GAG	CAC	AGC	TTG	TAG	СТС	CAG					684
	Arg																			185

Fig. 9

							ŤGΔ	CTG	GTC	TCC	ATC	CTC	TGG	AGC	TCC	GAC	GTG	CTC	611	39
			4.57.4	AAC	C C A															.99
CTC	GGA	GAC	AIA	AAU	CCA	611	CII	010	CIA	ЛСС	010	0,1,1	000	• • • • • • • • • • • • • • • • • • • •						
						0.00.4	000	ccc	_С СТ	ccc	ררר.	CCC	ፐገል	ccc	AGG	AAC	CGG	CCC	CTG	159
CTG	GCG	TCT	AAC	AGA	GAA	GIA		000	001	C1	Dec	Clu	Thr	Pro	Λτσ	Asn	Arg	Pro	Leu	. 20
eu	Ala	Ser	Asn	Arg	Glu	Val	Arg	613	710	ыу	LIO	013	1111	110	WIP	,,,,,,	6			•
									0.57.4	000	ር ም C	ccc	CCC	٨٥٥	ccc	TCC	TAT	AAG	CAC	219
CTG	CCC	CTG	CTG	CTG	CTT	CTG	CTU	116	CIA.	CLG	1	Dec	410	Sor	Ala	Trn	Tyr	lvs	His	40
leu	Pro	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Гел	L10	ren	F10	Ala	261	NIG	11.5	1 3 1	2,3		
	-						1		007	CCT	000	TCC	222	CTC	CTC	ATG	000	ста	CGC	279
GTG	GCG	AGT	CCC	CGC	TAT	CAC	ACA	616	661	L01	410	100	Cly	Lau	lan	Met	Glv	Len	ATE	60
Val	Ala	Ser	Pro	Arg	Tyr	His	Thr	Val	613	Arg	Ala	261	013	Lea	LCU	1000	013			
							0.07	000	ር ፕር	ccr	ccc	ርርፕ	ርቦፐ	CGA	000	CTC	TCC	CGG	CTC	339
CGC	TCG	CCC	TAC	CAG	TGG	CGC	CGI	666	616	Class	Class	412	412	Glv	Pro	l.eu	Ser	Arg	Leu	80
Arg	Ser	Pro	Tyr	Gln	Trp	Arg	AIg	Ala	ren	GIY	GIY	NIG	ліс	013	,,,	בסכ	<i>-</i>			
					000	ccc	ССТ	e T C	CTC	CTT	ССТ	ፐርር	TCA	GGG	CAG	GAG	CTG	TGG	GAG	399
CCA	GGA	CCG	GTC	GCC	CGC	000	41.	1.00	610	ננט	Dro	Ser	. Set	Glv	Gli	Glu	Leu	Trp	Glu	100
Pro	Gly	Pro	Val	Ala	Arg	613	Ala	LEU	Leu	Ten	110	561	501	0,,	0	,			Glu	
						c C T		ccc	רדז	רכר	CTC	' ГАТ	r GCA	CCC	TGC	G AGT	000	CGC	GAC	459
GTA	CGA	AGU	, AGU	AGU	C	D	. Ala	Cla	ים ל	Dro	Val	His	: Ala	Pro	Tri	Sei	Pro	Are	g Asp	120
Val	Arg	Sei	Arg	Ser	. Set	PIO	A 1 a	נוט ו	Len	110	161	11.1.5	, ,,,,							
						ccc		. ra/	: ፕሮር	. CT/	A G f	· CTI	r ca(. TC	TG(G ATO	TCA	GA(G GAG	519
CTG	GAG	i GG/	A GTO	: 666	CAR	. UUU	Cla	, C1+	, Car	. lai	, Sei	r lei	ı His	s Sei	r Tri	p 11e	e Sei	- G}1	u Glu	140
Leu	Glu	GI	y Val	ATE	3 611	ויונ	ונט נ	נוט נ	1 261	LCI	, 501	Dec		,						
					. TT				ጉ ሮሞ1	ר ממ	ተ ርርረ	ጉ ፖልሰ	ם ממו	A TGO	G TT	C CT	G CAG	G CA	A GTC	579
CCC	GCI	GC'	T AG	A GCI	יות נ	, 66/	i GAC	ያ <i>ጸ</i> ር(. ፕኤ	. 10		, UC	יתט כ	n Pri	n Tri	n Ph	e Lei	ı G1:	n Gli	n Val	160
Pro	Ala	A A l	a Ari	g Ala	a Phe	6 617	y 631	ותו נ	Lei	ווא נ	5 MI4	4 611	11 11,		P • •				n Val	
									~ A A I		4	r rr	r rr	ι ΓΔ	T GC	T TG	A CC	T AG	G CAC	639
)TA	TT	r GC	C GA	T CC	j GT(AG	انانا و	L AAI	AAI ن	- 1	- T-	o 00	~ D+	o un	. 00 e A1	. , 5 a ± ±	JJ		G CAC	176
				р Рг				o Ly	s Asi	n Ar	g it	h Wi	R ll	0 111	ות פ	יים ט	•			659
CAC	CAL	r 10	r TT	G AA	G CT	C CA														00.

Fig. 10



GPR8 ligand (log [M])

Fig. 11

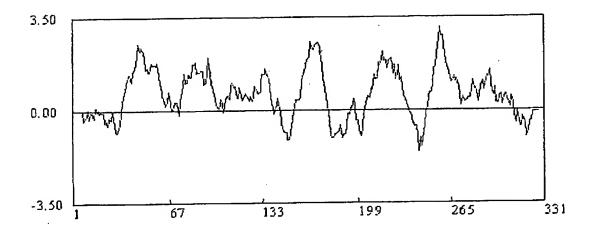


Fig. 12

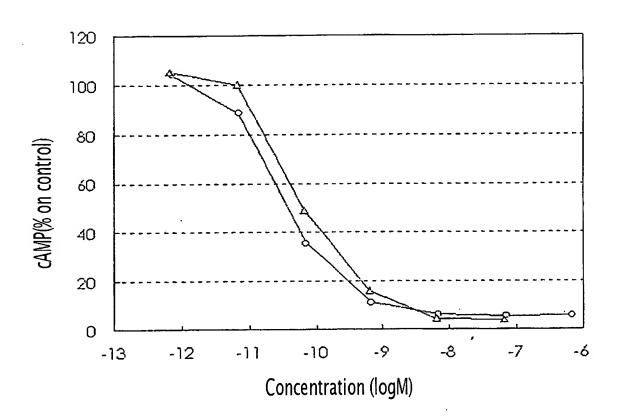


Fig. 13

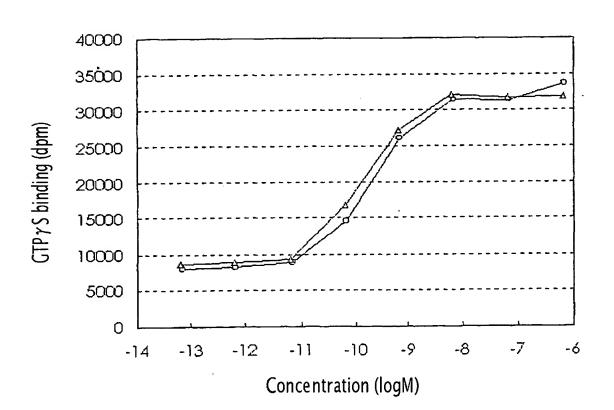


Fig. 14

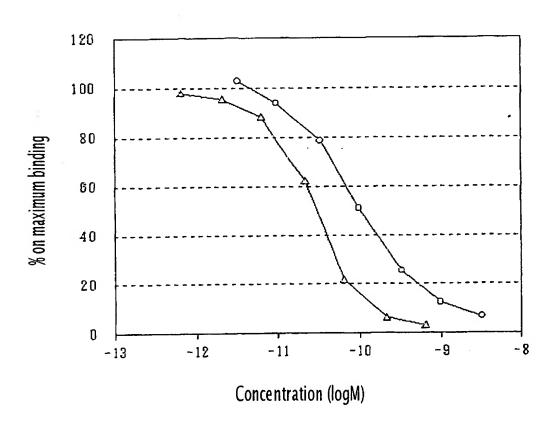


Fig. 15

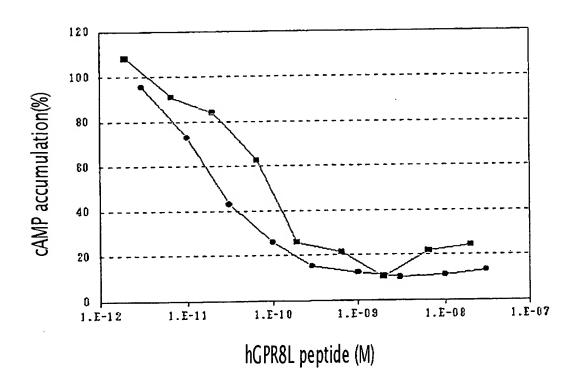


Fig. 16

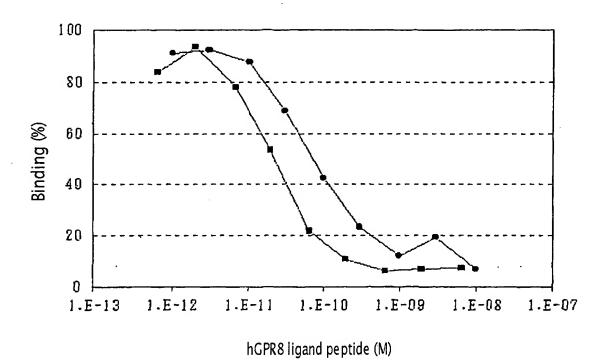


Fig. 17

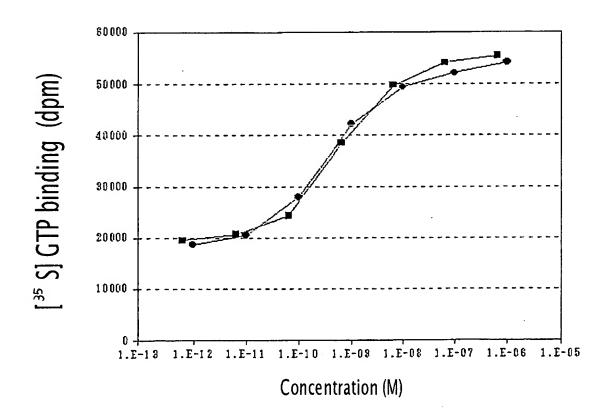


Fig. 18

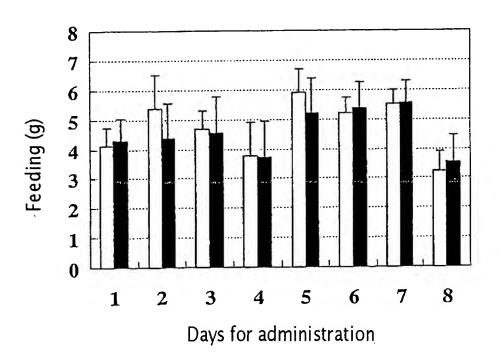


Fig. 19

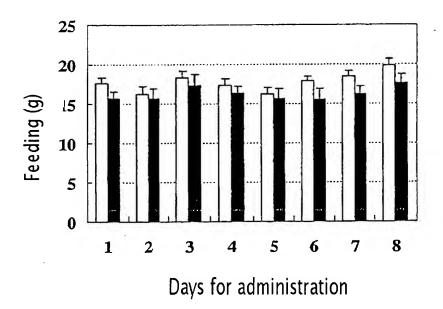


Fig. 20

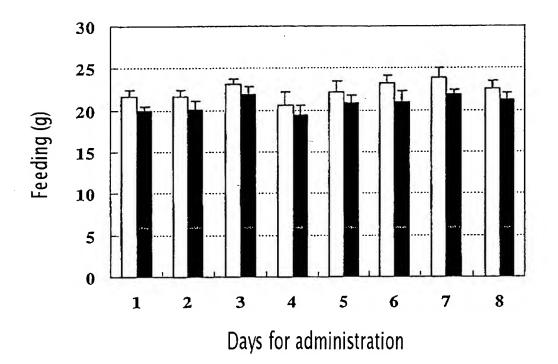
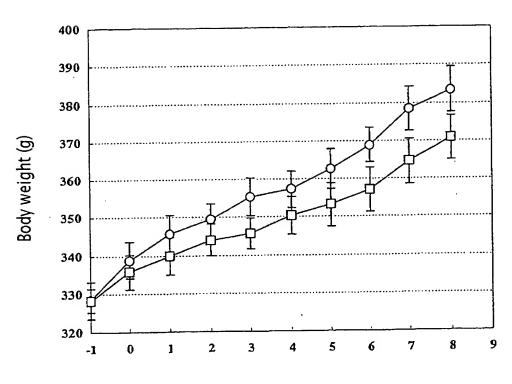
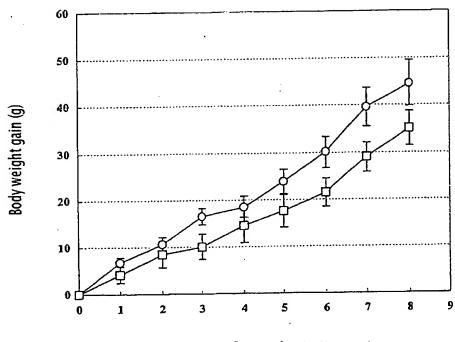


Fig. 21



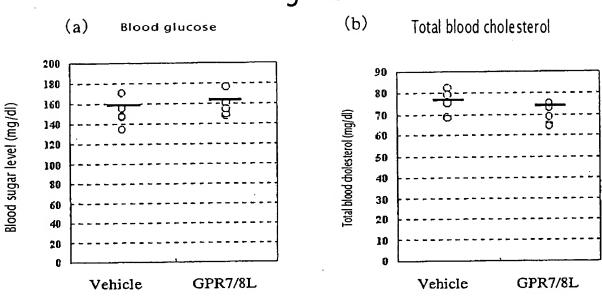
Days for administration

Fig. 22



Days for administration





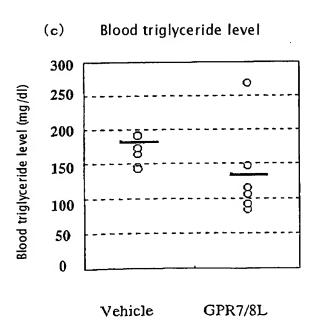


Fig. 24

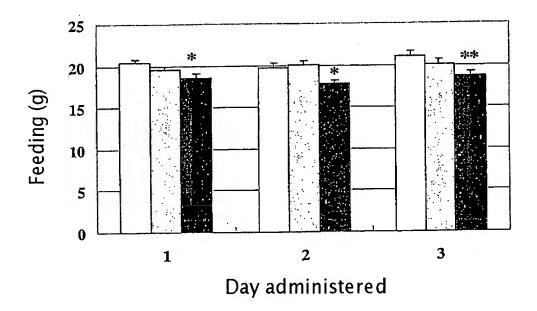


Fig. 25

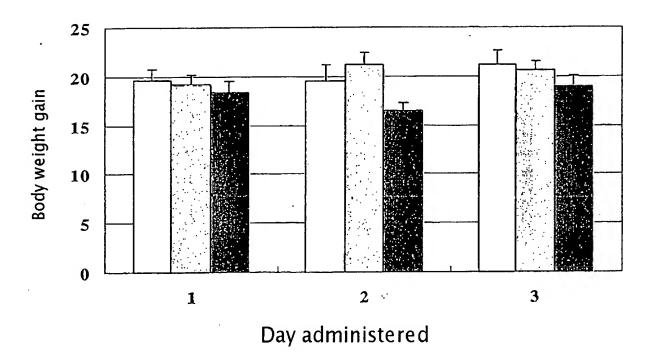


Fig. 26

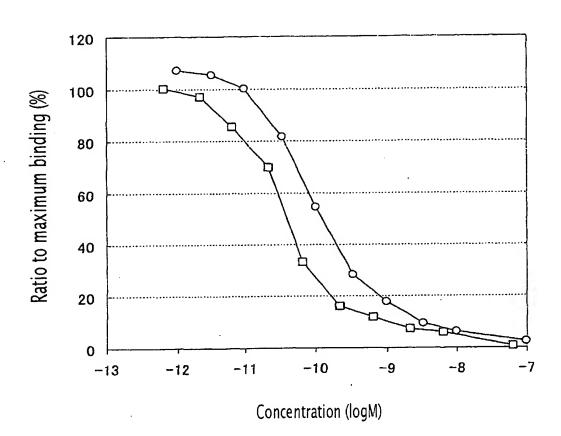


Fig. 27

